REMARKS

The Rejections Under 35 USC Section 102(e)

With regard to the Examiner's rejection of claims 1,2,4-7,9,11,13,14,17-27,29,30,34,36, and 37, under Section 102(e) as being anticipated by U.S. Pat. No. 6,312,725 to Wallace et. al. ("Wallace '725"), Applicants have amended claims 1,2,19,28, and 37 in order to overcome the rejections. Applicants acknowledge that Wallace '725 discloses biocompatible two part gel-forming polymer compositions but would respectfully like to point out and emphasize that the first component is dispersed in a liquid medium, while the second component may be either in a liquid medium or solid (i.e. powder) phase. Thus the possible phase choices are liquid-liquid or liquid-solid. By contrast, amended claims 1,2,19,28, and 37, and those claims depending therefrom, have now been limited to claim biphasic compositions comprising an aqueous phase and oil phase. Since aqueous/oil compositions are not disclosed in Wallace '725, the amendments to the claims have taken the invention out of the ambit of this reference. Applicants , having amended the claims so that they now no longer reading on Wallace'725, respectfully request withdrawl of this rejection.

The Rejections Under 35 USC Section 103

The Examiner had rejected claims 1 through 37 as unpatentably obvious over Wallace'725 in view of U.S. Pat. No. 5,498,421 (Grinstaff et al.). Applicants strongly contest the rejection and argue the non-obvious of the instant Invention based on essential distinctions that make the Invention non-obvious over the combination of these two references. The Examiner contends that Wallace (discussed above) is deficient (for purposes of rejecting under Section 103) in not disclosing the

compositions in the form of emulsions. The Examiner asserts that Grinstaff, teaches compositions in the form of emulsions, making the modification of Wallace's teaching in light of Grinstaff (and therefore the Invention) obvious. However, the Examiner misconceives the Invention. The invention provides biphasic compositions, now limited further by this Amendment and Response to compositions comprising an aqueous phase and an oil phase, in which the oil phase *not encased in any shell* is combined with an aqueous phase to form an emulsion. By contrast, Grinstaff teaches an "oil" surrounded by a polymer shell. As stated specifically in col. 7 lines 15-18,

> *"the present invention overcomes the drawbacks of the prior art by providing 1) injectable suspensions of polymeric shells containing biologic, 2) biologics in a form having enhanced stability compared to simple emulsions, ...".*

The polymeric shells alluded to which are to encase the oil (among other possible biologics) are described in numerous Examples (1,2,3,6, and 7, among many others). Therefore, because the combination of Grinstaff and Wallace would yield biphasic emulsions encased in polymeric shells, but not of a direct oil and water emulsion as in the Invention, and furthermore, because as the excerpt of Grinstaff col. 7 lines 15-18 above reveal, Grinstaff was intended to provide enhanced stability over simple emulsions and therefore actually *teaches away* from the idea of an emulsion not so encased in a polymeric shell.

Furthermore, when Grinstaff speaks of cross linking of the matrix (col. 6, lines 14-16) it is clear that this crosslinking takes place using functional groups in the polymeric shell (i.e. disulfide bonds). The Invention, by contrast, has no polymeric shell and the cross linking takes place utilizing functional groups present in the aqueous polymer, normally in the aqueous phase (page 3, line 9 et seq. of the specification). The biophysical properties and biologic release properties of an oil phase without a polymeric shell in an aqueous phase according to the Invention would not have been predictable. For

example, matrices according to the Invention have a texture with elasticity like rubber or gum, unlike the crosslinked polymeric shells of the prior art. Accordingly, the Invention is not made obvious by the combination of Wallace in light of Grinstaff and Applicants respectfully request withdrawal of the rejection.

Fees

No fees are believed to be required for this Preliminary Amendment. However, should any fees be necessitated hereby, authorization is hereby given to charge Deposit Account no. 11-1153 for any underpayment.

CONCLUSION

Entry of the foregoing remarks into the record of the above identified application is respectfully requested. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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Enclosure: Marked-Up Version of Amendment

PATENT
601.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Stanley Stein *et al*

SERIAL NO. : 09/883,842 EXAMINER: L. DI NOLA BARON

FILED : June 18, 2001 ART UNIT : 1615

FOR : MULTIPLE PHASE CROSS-LINKED COMPOSITIONS AND USES THEREOF

AMENDMENT AND RESPONSE
VERSION WITH MARKINGS TO SHOW CHANGES

1 (Amended) A pharmaceutical composition comprising a matrix capable of delivering at least one therapeutic agent to a bodily compartment under controlled release conditions, said matrix comprising a homogeneous mixture of aqueous phase and [at least one other phase] oil phase, at least one therapeutic agent present in at least one of said phases, and at least one cross-linked polymer physically entrapping said at least one therapeutic agent.

19. (Amended) A method for preparing the pharmaceutical composition of claim 1 comprising the steps of

i) preparing a mixture comprising at least one therapeutic agent and [at least] two phases, one of which is an aqueous phase and the other an oil phase, said aqueous phase comprising a polymer having at least two functional groups thereon;

ii) cross linking said polymer under conditions to form a cross-linked matrix having said therapeutic agent trapped therein.

28. (Amended) The method of claim 25 wherein said controlled release conditions occur as a consequence of diffusion from said matrix or biodegradation of said matrix by an in-vivo degradation pathway selected from the group consisting of reducing agents, reductases, two or more thiol groups, [and a plurality of phases, one of which is] an aqueous phase and an oil phase, a cross-linking agent comprising two or more thiol-reactive groups, and a therapeutically effective amount of drug; and injecting said mammal with said solution whereby a hydrogel drug depot is formed at the site of injection having said drug temporarily entrapped therein.

37. (Amended) A hydrogel composition comprising a homogenous mixture of aqueous phase and [at least one other phase] oil phase and at least one cross-linked polymer in one of said phases.